AWARD NUMBER: W81XWH-14-1-0540

TITLE: Phase 0 Trial of Itraconazole for Early-Stage Non-Small Cell Lung Cancer

PRINCIPAL INVESTIGATOR: David E. Gerber, MD

CONTRACTING ORGANIZATION: UNIVERSITY OF TEXAS SOUTHWESTERN MEDICALCENTER
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Fort Detrick, Maryland 21702-5012

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Phase 0 Trial of Itraconazole for Early-Stage Non-Small Cell Lung Cancer

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**5b. GRANT NUMBER**
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**6. AUTHOR(S)**

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**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

University of Texas Southwestern Medical Center
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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

The overall objective of this phase 0 clinical trial is to determine the pharmacodynamic effects of itraconazole. Itraconazole—an antifungal agent in clinical use for decades—has shown promise as a lung cancer therapy with broad applicability, excellent safety, and a cost one-tenth that of many emerging lung cancer treatments. We have shown that itraconazole has anti-angiogenic properties, inhibits the Hedgehog (Hh) pathway (which plays a fundamental role in cancer stem cell biology), and results in tumor regression in preclinical models. Thus, the specific aims of this project are the following: (Aim 1) Determine effects of itraconazole on tumor angiogenesis; (Aim 2) Determine effects of itraconazole on the Hh pathway; (Aim 3) Determine effects of itraconazole pharmacokinetics (PK) on the pharmacodynamic profile of itraconazole. These aims are achieved through a set of blood-, tissue-, and skin-based biomarkers. Over the past 12 months of this trial, we have continued to enroll patients on the anticipated schedule and performed preliminary imaging, PK, and PD analyses.

**15. SUBJECT TERMS**

Nothing listed

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| U | U | U | UU | 11 | 19b. TELEPHONE NUMBER *(include area code)* |

**Table of Contents**

**Page**

## 1. INTRODUCTION:

The objective of the proposed project is to determine the biologic effects of the drug itraconazole on lung cancer. Itraconazole is a well-tolerated and inexpensive (less than 10% the cost of recently developed molecularly targeted therapies) drug that has been in use for decades to treat fungal infections. Laboratory studies have shown that it also appears to block the growth of cancer through effects on tumor blood vessels (angiogenesis) and by targeting the Hedgehog developmental/survival pathway. In this clinical trial, 15 patients with early-stage lung cancer planned for surgical resection will receive approximately two weeks of itraconazole therapy. Before and during their treatment, they will undergo tissue and blood sampling in addition to magnetic resonance imaging (MRI) scans for biomarker analysis. At the time of surgery, resected tissue will be analyzed for similar biomarkers. These tissue, blood, and imaging biomarkers will be analyzed to determine itraconazole levels, effects on tumor blood vessels, effects on the Hedgehog pathway, and the correlation between each of these endpoints.

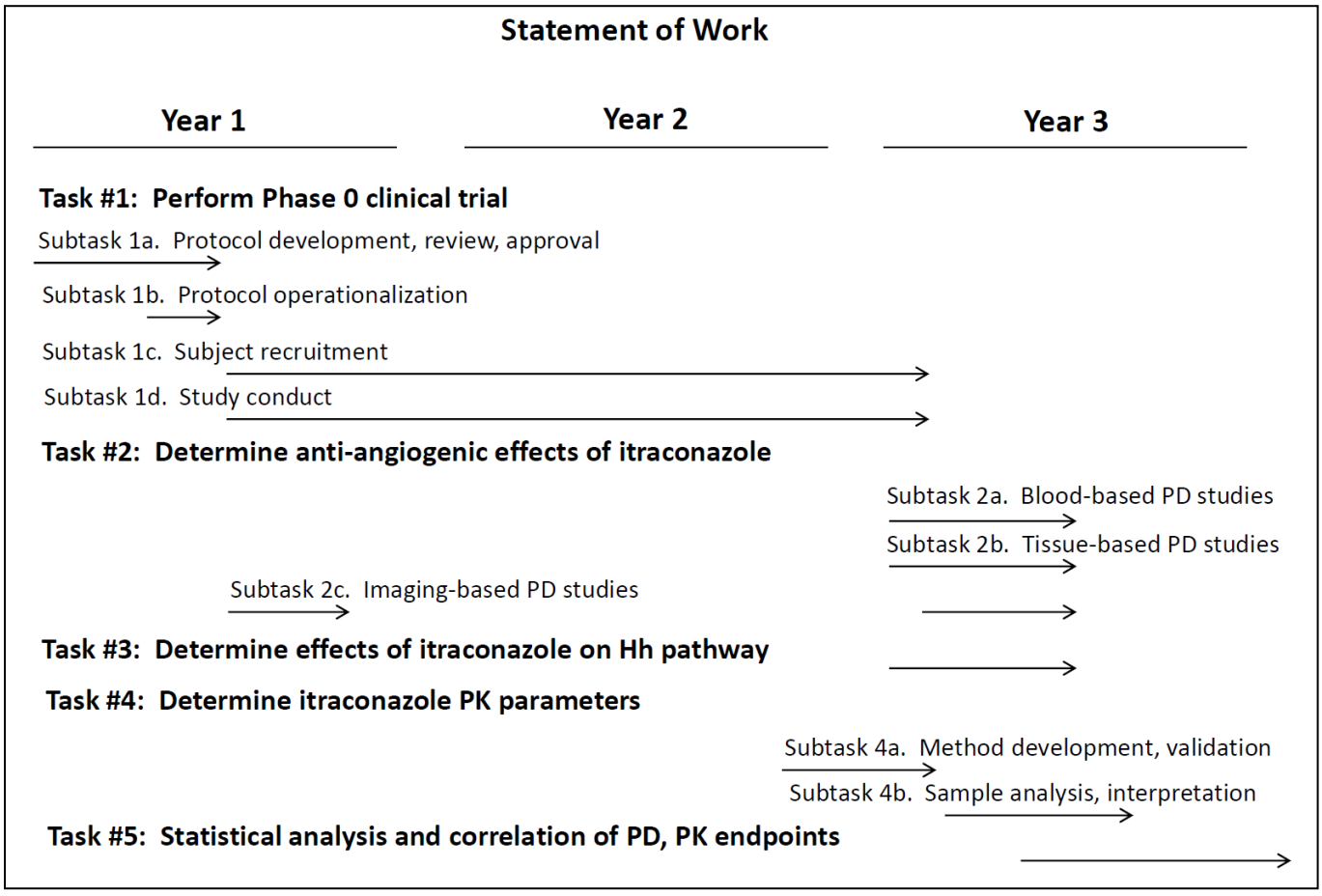
## 2. KEYWORDS:

lung cancer; itraconazole; repurposing; Hedgehog pathway; stem cell; angiogenesis; neoadjuvant; pharmacodynamic; pharmacokinetic.

## 3. ACCOMPLISHMENTS:

Year 1 Progress Report. Original Statement of Work printed below.

A. **What were the major goals of the project**?



B. **What was accomplished under these goals**?

**Task 1: Perform Phase 0 Clinical Trial**

**Subtask 1a:** Protocol Development, Review, Approval

A full protocol was developed by Study Chair and PI Dr. David Gerber, in conjunction with UT Southwestern faculty member Dr. Lorraine Pelosof. The full protocol and informed consent form were approved by the UT Southwestern Harold C. Simmons Comprehensive Cancer Center Protocol Review and Monitoring Committee (PRMC) on January 22, 2015. The full protocol and informed consent form were approved by the UT Southwestern IRB on March 17, 2015 (STU 122014-038). Provisional approval was received by the Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) (Proposal Log Number LC130650, Award Number W81XWH-14-1-0540, HRPO Log Number A-18295) on May 19, 2015. The protocol was activated at UT Southwestern Medical Center and Parkland Health and Hospital System in June 2015, approximately two months after our initial goal of April 2015.

**Subtask 1b:** Protocol Operationalization

During the first 6 months of the award period (October 2014-April 2015), I convened regular meetings with all involved parties. This included representation from the Clinical Research Office; Departments of Radiology, Thoracic Surgery, Pulmonary Medicine, Hematology-Oncology; Texas Tech School of Pharmacy; Hamon Center for Therapeutic Oncology Research; and the Biomarker Research Core.

We established Standard Operating Procedures for all study procedures. We ordered all required supplies for study procedures.

**Subtask 1c:** Subject Recruitment

Recruitment began in earnest in July 2015. As this is the first window-of-opportunity trial in lung cancer to be performed at UT Southwestern Medical Center, we were required to educate and encourage our colleagues in the Thoracic Surgery Program. Patients with early-stage lung cancer generally are not evaluated by medical oncology prior to surgical resection. We met with these physicians, mid-level providers, and clinic nurses. We prepared "cheat sheets" for these individuals that contained contact information and a basic description of study eligibility. We pre-screened patients referred to the thoracic surgery faculty. We reminded clinicians of the trial at weekly thoracic oncology tumor boards.

By the end of the first year of the award period, we had accrued a total of 2 patients. We have currently accrued a total of 8 patients, thereby averaging one new patient accrual every two months. This pace of accrual attests to the ongoing and substantial efforts of the clinical research team to educate all relevant providers and promote the trial. Based on this success, we anticipating achieving full enrollment and completing the scientific objectives by the end of the study period.

**Subtask 1d:** Study Conduct

Eight patients have been enrolled as of this annual report. Their baseline characteristics are displayed in the table below. All identifiers have been removed.

| Study Number | Age | Gender | Race | Ethnicity | Smoking Status | Pack Years |
|---|---|---|---|---|---|---|
| 7701 | 63 | Male | Caucasian | Non-Hispanic | Former | 40 |
| 7702 | 64 | Female | Caucasian | Non-Hispanic | Former | 47 |
| 7706 | 50 | Female | Caucasian | Non-Hispanic | Former | Unknown |
| 7707 | 69 | Male | Caucasian | Non-Hispanic | Former | 25 |
| 7708 | 62 | Female | Caucasian | Non-Hispanic | Never | N/A |
| 7709 | 77 | Female | Caucasian | Non-Hispanic | Former | 4 |
| 7710 | 51 | Male | Caucasian | Non-Hispanic | Never | N/A |
| 7711 | 80 | Male | Caucasian | Non-Hispanic | Former | 30 |

As described in the original proposal, these subjects underwent study-related MRI scans, skin biopsies, blood tests, treatment with itraconazole, and surgical resection. To date, there have been no complications encountered with any clinical procedures. All patients have completed itraconazole administration, surgical resection, serial blood sampling, and serial skin biopsies. Due to either contraindications or scanner status, two of the eight patients did not complete serial MRIs scans.

**Task 2: Determine anti-angiogenic effects of itraconazole**

**Subtask 2a:** Blood-based PD studies

As described in the original Statement of Work, this subtask is planned to be performed during Year 3 of the project. During that period, we will batch samples and perform a multiplex cytokine assay to determine the effects of itraconazole on factors related to tumor angiogenesis.

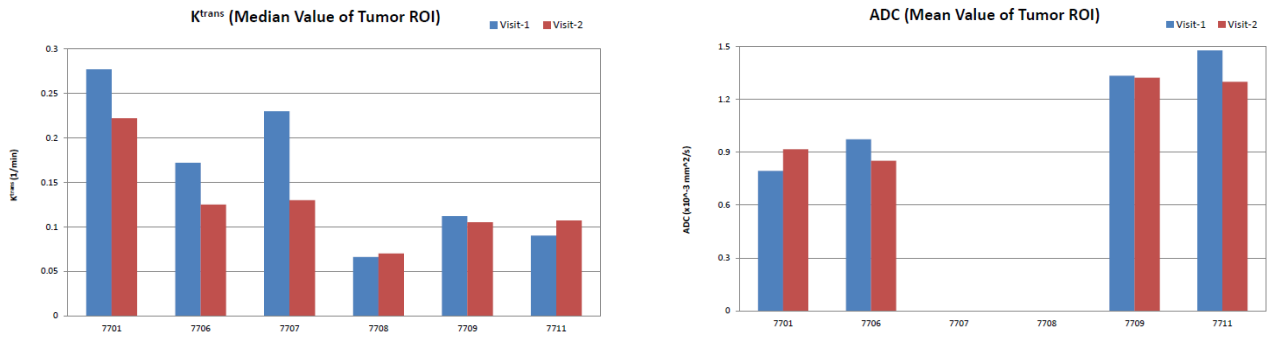
**Subtask 2b:** Tissue-based PD studies

As described in the original Statement of Work, this subtask is planned to be performed during Year 3 of the project. We have collected the required archival and post-treatment tissue specimens and will be performing the planned correlative studies in early 2017.

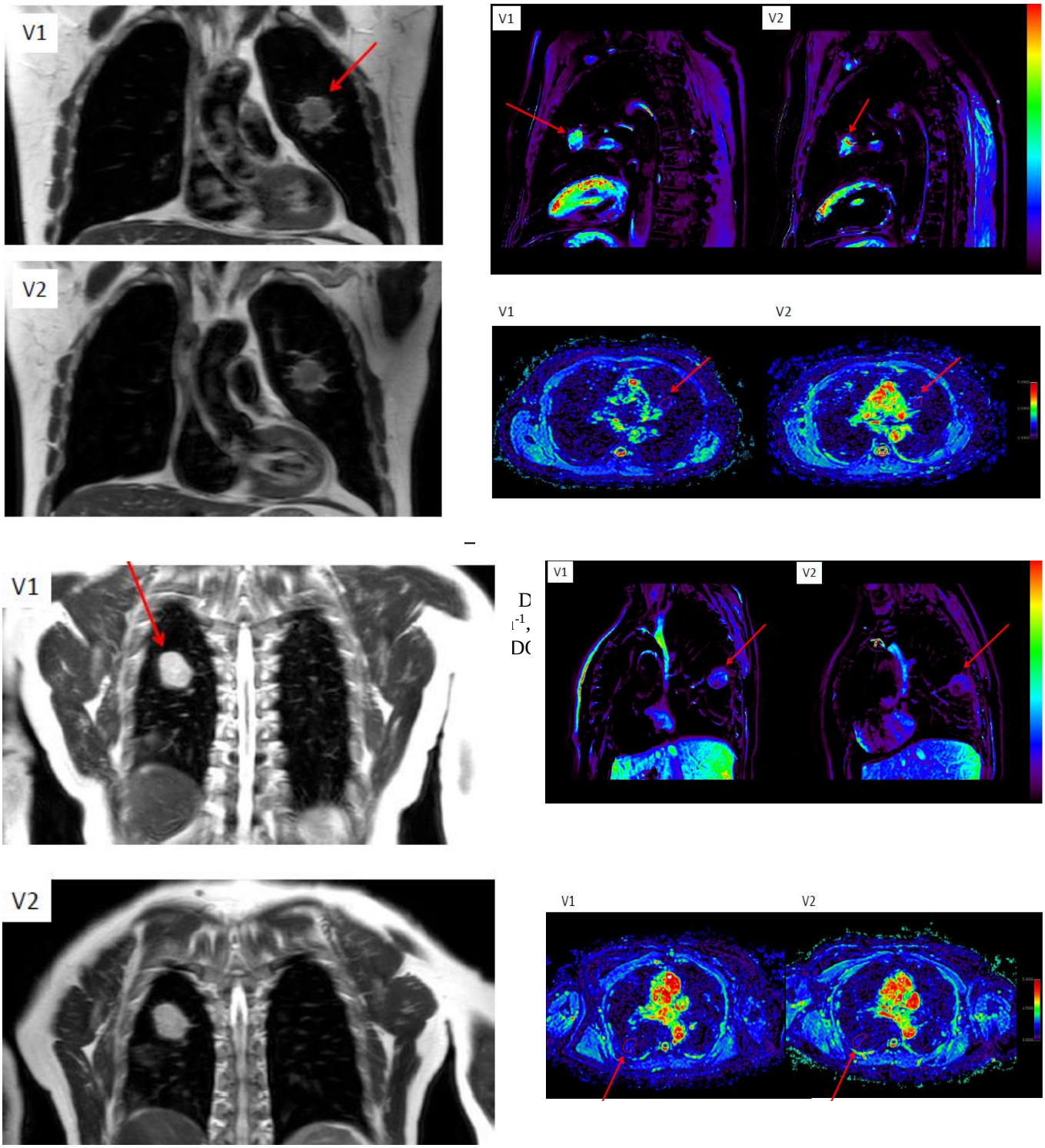
**Subtask 2c:** Imaging-based PD studies

We have performed pre- and post-treatment research multiparametric MRI scans on 6 of the 8 enrolled patients. Methods are summarized as follows: we used a 3T MRI scanner (Ingenia, Philips Healthcare) with anterior and posterior torso coils. The following images were obtained: (1) T2-weighted anatomic imaging; (2) Diffusion Weighted Imaging (DWI)-Apparent Diffusion Coefficient (ADC) (for which there was good image quality in 4 patients; (3) Dynamic Contrast Enhanced (DCE) MRI-vascular permeability measure, $K^{trans}$ (Tofts model). The Region of Interest (ROI) of the tumor was defined on the central slice of the tumor. Pixel-by-pixel values of $K^{trans}$ and ADC were measured.

Available summary data are shown below:




***Left*** Change of tumor vascularity. ***Right*** Change of tumor diffusivity

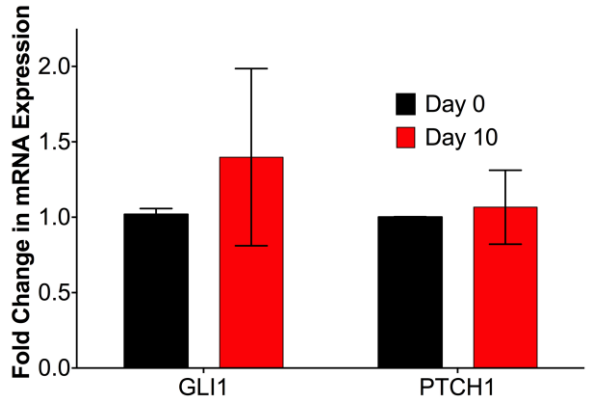



***Left*** Pre- and post-treatment T2-weighted images ***Top Right*** DCE-MRI. Pre-treatment $K^{trans}$ mean = 0.167 min-1, $K^{trans}$ median = 0.172 $min^{-1}$. Post-treatment $K^{trans}$ mean = 0.123 $min^{-1}$, $K^{trans}$ median = 0.125 min-1. ***Bottom Right*** ADC-MRI. Pre-treatment ADC mean = 0.974 x $10^{-3}$ $mm^2/s$. Post-treatment ADC mean = 0.853 x $10^{-3}$ $mm^2/s$.

**Task 3: Determine effects of itraconazole on Hh pathway**

Although not planned until Year 3 of the project, we have initiated these studies on serial skin biopsy specimens from the initially enrolled patients to confirm adequacy of collection and processing techniques. As of this report,

we have performed mRNA analysis of target biomarkers in serial skin biopsies from the first 7 enrolled patients (see below). Tumor tissue analysis is forthcoming.




mRNA expression of GLI1 and PTCH1 from serial skin biopsies from first 7 enrolled patients.

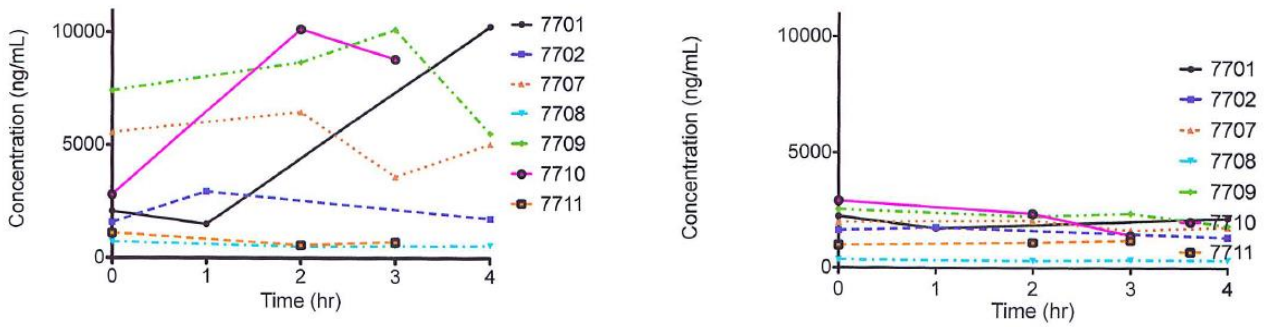
**Task 4: Determine itraconazole PK parameters**

**Subtask 4a:** Method development, validation

Our collaborators at the Texas Tech School of Pharmacy have developed and are validating PK methods for itraconazole and the principal metabolite, itraconazole-OH. To date, they have performed these assays in the first 7 enrolled patients.

**Subtask 4b:** Sample analysis, interpretation

We have completed analysis of itraconazole and itraconazole-OH in the first 7 enrolled patients. Summary data is shown below. As evident from the figures, there is considerable interpatient variation. Tissue-based PK analysis have not yet been performed but are planned for Year 3.




***Left*** Itraconazole PK analysis ***Right*** Itraconazole-OH analysis

**Task 5: Statistical analysis and correlation of PD, PK endpoints**

Planned for Year 3 of project.

C. **What opportunities for training and professional development has the project provided**?
Nothing to report.

D. **How were the results disseminated to communities of interest**?
Nothing to report.

E. **What do you plan to do during the next reporting period to accomplish the goals**?
Nothing to report.

**4. IMPACT:**

A. **What was the impact on the development of the principal discipline(s) of the project**?
Nothing to report.

B. **What was the impact on other disciplines**?
Nothing to report.

C. **What was the impact on technology transfer**?
Nothing to report.

D. **What was the impact on society beyond science and technology**?
Nothing to report.

**5. CHANGES/PROBLEMS:**

A. **Changes in approach and reasons for change**
Nothing to report.

B. **Actual or anticipated problems or delays and actions or plans to resolve them**
Nothing to report.

C. **Changes that had a significant impact on expenditures**
Nothing to report.

D. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
Nothing to report.

E. **Significant changes in use or care of human subjects**
Nothing to report.

F. **Significant changes in use or care of vertebrate animals**
Nothing to report.

G. **Significant changes in use of biohazards and/or select agents**
Nothing to report.

**6. PRODUCTS:**

A. **Publications, conference papers, and presentations**
Nothing to report.

B. **Website(s) or other Internet site(s)**
Nothing to report.

C. **Technologies or techniques**
Nothing to report.

D. **Inventions, patent applications, and/or licenses**
Nothing to report.

E. **Other Products**
Nothing to report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

A. **What individuals have worked on the project**?

| **Participant Names:** | **Role/Contribution:** |
|---|---|
| David Gerber, MD (PI) | No change |
| James Kim, MD (Hh pathway analysis) | No change |
| Richard Leff, MD – Texas Tech (PK analysis) | No change |
| Claudia Meek – Texas Tech (PK analysis) | No change |
| Rolf Brekken, PhD (co-investigator/planning) | No change |
| Kemp Kernstine, MD (co-investigator/planning) | No change |
| Robert Lenkinski, MD (co-investigator/planning) | No change |
| Chul Ahn, PhD (co-investigator/planning) | No change |

B. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

**Change in active support for the PI:** New grants since submission of grant proposal.
David Gerber

1K24CA201543-01 (PI: Gerber) 05/01/2016-04/30/2021 6.0 calendar months
NIH-National Cancer Institute
Midcareer Award in Patient-Oriented Research (Parent K24)
Development of New Cancer Treatments and Investigators
Goals: To conduct independent patient-oriented research and help develop the next generation of patient-oriented researchers.

2P30CA142543 (PI: Gerber) 09/01/2016-08/31/2017 0.6 calendar months
NIH-National Cancer Institute
*CCSG Supplement Year 7 – Immunotherapy Biomarkers*
Goals: The CCSG provides support for senior leadership, five scientific research programs, six shared resources, protocol specific research, protocol review and monitoring, planning and evaluation activities, developmental funds, and administration to promote innovations in cancer diagnosis, treatment and control and builds on the outstanding science and the tradition of excellence in clinical training at UTSW.

*No overlap in any listed proposals with the current Dept. of Defense project.*

C. **What other organizations were involved as partners?**
Organization Name**:** Texas Tech University School of Pharmacy
Location of Organization**:** Dallas Texas
Partner's contribution to the project:
Collaboration: Dr. Leff and Dr. Meek are performing PK analysis

**8. SPECIAL REPORTING REQUIREMENTS**
Nothing to report.

**9. APPENDICES:** References listed in the annual report.

**REFERENCES:**


Aftab, B.T., et al., *Itraconazole inhibits angiogenesis and tumor growth in non-small cell lung cancer.* Cancer Res, 2011. **71**(21): p. 6764-72.

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